REMARKS

The Office Action of June 23, 2003 has been received and its contents carefully considered.

Claims 14 to 29 are all the claims pending in the application.

The present application is the National Stage of an International Application. The International Bureau forwarded copies of an International Search Report and the reference cited therein to the U.S. Patent Office, as shown in the Notice of Acceptance mailed on April 25, 2002, which indicates that the U.S. Patent Office received a copy of the International Search Report and a copy of the references cited in the International Search Report. Applicants are submitting concurrently herewith an Information Disclosure Statement with a Substitute Form PTO-1449 listing each of these references.

The Examiner acknowledges applicants' election of Group XV, directed to claims 14-29, and applicants' election of verapamil as the second drug. The Examiner also acknowledges applicants' species election.

The Examiner states that he has searched for the elected species, but did not find any prior art to reject applicants' elected species. The Examiner states that the search, therefore, was extended over the full scope of the elected group, but has not been extended beyond the elected group. The Examiner, therefore, requests applicants to cancel all non-elected subject matter.

Applicants understand this requirement to mean that the Examiner is requesting that applicants should amend all of the claims to limit them to verapamil as the second drug, and that the recitations in the claims that are directed to other compounds as the second drug be canceled.

Applicants defer making the amendments until a later time in the expectation that the Examiner will find allowable subject matter and extend the search to non-elected subject matter.

Claims 19-26 have been rejected under the first paragraph of 35 U.S.C. §112 as being based on a non-enabling disclosure.

The Examiner asserts that the specification does not provide an enabling disclosure for the derivatives of the compounds recited in claims 19 and 26.

In response, applicants have amended the claims to delete references to "derivatives". For example, instead of reciting "bisaminothiol or its derivatives", the claims have been amended to recite "a bisaminothiol compound".

In view of the above, applicants request withdrawal of this rejection.

Claims 19 and 26 have been rejected under the second paragraph of 35 U.S.C.§112 as indefinite.

The Examiner states that the phrase "derivatives" and the phrase "analog" are indefinite.

As discussed above, applicants have amended the claims to delete the phrase "derivatives".

Further, these claims do not contain the phrase "analog".

In view of the above, applicants request withdrawal of this rejection.

Claims 14-17, 20, 21, 23, 25, 28 and 29 have been rejected under 35 U.S.C. §102(b) as anticipated by Pritchard et al.

Applicants submit that Pritchard et al do not disclose or render obvious the presently claimed invention and, accordingly, request withdrawal of this rejection.

The present invention, as set forth in claim 14, is directed to a method of administering a drug with binding affinity for plasma protein, wherein, in the administration of a first drug with binding affinity for plasma protein, a single or plural second drug with binding affinity for the same plasma protein for which the first drug has binding affinity, is administered simultaneously with the first drug or before or after the administration of the first drug to thereby regulate the binding of the first drug to the plasma protein.

In another aspect, as set forth in claim 21, the present invention is directed to a pharmaceutical preparation for regulating binding affinity of a first drug for plasma protein, which comprises a first drug with binding affinity for plasma protein and a single or plural second drug with binding affinity for the same plasma protein, for which the first drug has binding affinity.

The Examiner states that Pritchard et al disclose plasma protein binding of bepridil using radiolabeled bepridil (bepridil-14C). The Examiner states that Pritchard et al disclose that the free fractions of bepridil were enhanced by the addition of verapamil, as disclosed in the abstract; page 348, column 2 "Effects of Other Drugs"; and page 351, Table V. The Examiner further

states that Pritchard et al disclose the addition of verapamil at ten- to 100-fold molar excess over bepridil resulted in significant displacement of bepridil from its plasma protein binding sites, as disclosed on page 351, left hand column, first complete paragraph.

The Examiner concludes that both the present invention and Pritchard et al disclose a pharmaceutical composition wherein a first drug (bepridil) is administered prior to the administration of verapamil.

In response, Pritchard et al disclose in vitro tests to investigate the plasma protein binding of bepridil. The abstract of Pritchard et al discloses that free fractions of bepridil were enhanced by addition of drugs such as (verapamil, nifedipine, dilteazem, disopyramide and warfarin), but only at concentration above those achieved clinically. On page 351, Pritchard et al disclose that there were no changes in bepridil plasma binding when the drugs were present at equimolar concentrations or less. On page 352, right hand column, Pritchard et al state that verapamil appears to displace bepridil if added in a ten or 100-fold molar excess, and that such a concentration is many times greater than that achieved clinically.

Accordingly, applicants submit that Pritchard et al do not disclose or suggest that verapamil can be used as a second drug to regulate the binding of bepridil, since the amount of verapamil necessary to affect the binding is greater than the amounts that are clinically employed. Therefore, applicants submit that Pritchard et al teach against a method of administering of drugs in accordance with the method set forth in the present method claims 14 to 20.

With respect to the pharmaceutical preparation set forth in claims 21-29, applicants note that Pritchard et al disclose a change in the plasma binding at an addition of verapamil at a 10 to 100 fold molar excess over bepridil. However, since Pritchard et al disclose that these amounts were not amounts that are clinically used, the preparations that Pritchard et al made, in fact, were not pharmaceutical preparations for regulating the binding affinity of the bepridil. Thus, the preparations made by Pritchard et al were not pharmaceutical preparations, but test preparations which would never, in fact, be employed as a pharmaceutical preparation.

In view of the above, applicants submit that Pritchard et al do not disclose or render obvious the presently claimed invention and, accordingly, request withdrawal of this rejection.

Claims 14-17, 20, 21, 23, 25, 28 and 29 have been rejected under 35 U.S.C. § 102(b) as anticipated by Somogyi et al.

Applicants submit that Somogyi et al do not disclose or render obvious the presently claimed invention and, accordingly, request withdrawal of this rejection.

The Examiner appears to be relying on three separate disclosures of Somogyi et al, each of which, according to the Examiner, satisfies the recitations of the present claims.

First, the Examiner asserts that Somogyi et al disclose that both an intravenous dose and an oral dose of verapamil are administered simultaneously. See page 51 where Somogyi et al disclose using a stable labeled oral solution of verapamil and simultaneous administration of an unlabelled intravenous dose of the drug. The Examiner asserts that the present claims do not

require that the two drugs be different, and that the disclosure in Somogyi et al of two different dosage forms of the same drug satisfies the recitations of the present claims.

In general, Somogyi et al do not discuss binding to plasma protein, but discuss other aspects of pharmacokinetics and bioavailability. The only mention of binding to plasma protein that applicants have found in Somogyi et al appears in item 4 of the abstract and in the "Discussion" at page 55, where Somogyi et al state that plasma protein binding remained unchanged. Applicants submit that this disclosure teaches away from the regulation of the binding.

The Examiner also relies on the fact that Somogyi et al disclose that antipyrine and indocyanine green were administered as a bolus dose to a patient that was being treated with verapamil.

Somogyi et al disclose, at page 54, that in all seven patients that were tested, the antipyrine saliva clearance was reduced from normal values and that the indocyanine green blood clearance was reduced.

Again, applicants do not see any discussion of regulation of protein binding. Clearance is not necessarily related to protein binding.

The Examiner also relies on the disclosure at page 59 of Somogyi et al that most of the patients being treated with verapamil were receiving cimetidine and/or spironolactone, and the statement in Somogyi et al at page 59 that the co-administration of these drugs with verapamil may have affected the bioavailability and oral clearance of verapamil.

This disclosure does not state that bioavailability and clearance were, in fact, affected, but only speculates that they may have been affected. Further, even if bioavailability and clearance were affected, this does not indicate that plasma protein binding was involved. Applicants do not see any discussion or disclosure of the regulation of protein binding.

In view of the above, applicants submit that Somogyi et al do not defeat the patentability of the present claims and, accordingly, request withdrawal of this rejection.

Claims 14 and 16-29 have been rejected under 35 U.S.C. §103(a) as obvious over Pritchard et al in view of Li et al.

Applicants submit that these documents do not disclose or render obvious the presently claimed invention and, accordingly, request withdrawal of this rejection.

In this rejection, the Examiner states that Pritchard et al fail to disclose a kit comprising a first and second drug, and other radiolabels and/or a chelator which may be conjugated to the drug.

The Examiner relies on the Li et al patent for a teaching of water-soluble polymer conjugate of "other therapeutic drugs" which include verapamil, and for a teaching of water-soluble pro-drugs. The Examiner states that the complexes in Li et al may be radiolabeled with various metals or conjugated to various chelators, and that the complexes may be imaged using single photo emission computer topography or positron emission tomograpy. The Examiner states that Li et al disclose that verapamil can be used in combination with another drug that may be radiolabeled.

The Examiner asserts that it would have been obvious to modify the invention of Pritchard et al by using the teachings of Li et al, and generate a kit comprising first and second drugs and attach various radiolabels and/or a chelators, because Li et al disclose a composition wherein verapamil may be added to generate a water soluble polymer conjugate.

Applicants have discussed Pritchard et al in detail above. Applicants rely on that discussion.

Thus, as discussed above, Pritchard et al disclose in vitro tests to investigate the plasma protein binding of bepridil. The abstract of Pritchard et al discloses that free fractions of bepridil were enhanced by addition of drugs such as (verapamil, nifedipine, dilteazem, disopyramide and warfarin), but only at concentration above those achieved clinically. On page 351, Pritchard et al disclose that there were no changes in bepridil plasma binding when the drugs were present at equimolar concentrations or less. On page 352, right hand column, Pritchard et al state that verapamil appears to displace bepridil if added in a ten or 100-fold molar excess, and that such a concentration is many times greater than that achieved clinically.

Accordingly, applicants submit that Pritchard et al do not disclose or suggest that verapamil can be used as a second drug to regulate the binding of bepridil, since the amount of verapamil necessary to affect the binding is greater than the amounts that are clinically employed. Therefore, applicants submit that Pritchard et al teach against a method of administering of drugs in accordance with the method set forth in the present method claims 14 to 20.

With respect to the pharmaceutical preparation set forth in claims 21-29, applicants note that Pritchard et al disclose a change in the plasma binding at a 10 to 100 fold molar access. However, since Pritchard et al disclose that these amounts were not amounts that are clinically used, the preparations that Pritchard et al made, in fact, were not pharmaceutical preparations for regulating the binding affinity of the bepridil. Thus, the preparations made by Pritchard et al were not pharmaceutical preparations, but test preparations which would never, in fact, be employed as a pharmaceutical preparation.

Turning now to Li et al, although the Examiner states that Li et al disclose that verapamil can be used in combination with another drug that may be radiolabeled, applicants have not found any such disclosure in Li et al. Li et al merely disclose that verapamil can be used to make a water soluble polymer conjugate, and that water soluble metal chelator conjugates of Li et al can contain a radionuclide in certain embodiments. Li et al disclose that the water soluble conjugates can be administered in conjunction with other drugs, but do not disclose that these other drugs may be radiolabeled.

In any event, Li et al do not supply the deficiencies of Pritchard et al that have been discussed above. Accordingly, the combination of Pritchard et al with Li et al would not have led one of ordinary skill in the art to the present invention.

In view of the above, applicants submit that the cited references do not defeat the patentability of the presently claimed invention and, accordingly, request withdrawal of this rejection.

Claims 14 and 16-29 are have been rejected under 35 U.S.C. § 102(b) as anticipated by Somogyi et al in view of Li et al. Applicants assume the Examiner intends this to be an obviousness rejection under 35 U.S.C. § 103.

Applicants submit that these references do not disclose or render obvious the presently claimed invention and, accordingly, request withdrawal of this rejection.

Applicants have discussed Somogyi et al in detail above, and rely on that discussion.

Thus, as discussed above, Somogyi et al do not discuss binding to plasma protein, but discuss other aspects of pharmacokinetics and bioavailability. The only mention of binding to plasma protein that applicants have found appears in item 4 of the abstract and in the "Discussion" at page 55, where Somogyi et al state that plasma protein binding remained unchanged. This disclosure teaches away from the regulation of the binding.

In addition, applicants have discussed Li et al above, and rely on that discussion.

Li et al do not supply the deficiencies of Somogyi et al that have been discussed above. Accordingly, the combination of Somogyi et al with Li et al would not have led one of ordinary skill in the art to the present invention.

In view of the above, applicants submit that the cited references do not defeat the patentability of the presently claimed invention and, accordingly, request withdrawal of this rejection.

The Examiner states that the present application is filed under former 37 C.F.R. 1.60, and lacks the necessary reference to the prior application. The Examiner states that a statement should be inserted at the first sentence of the specification indicating that this is a 371 application.

Applicants do not understand why the Examiner refers to former 37 C.F.R. 1.60. The present application was not filed under this rule, but was filed as the National Stage entry of the PCT application. Further, the MPEP makes it clear that applications that are the National Stage Entry of a PCT application do not have to contain, as a first sentence, a reference to the PCT application. See MPEP § 1893.03(c), page 1800-156, of Rev. 1, Feb 2003, of the Eighth Edition. Accordingly, applicants request withdrawal of this requirement.

The Examiner set forth three proposed amendments to the claims (claim 17 (correction of a typographical error) and claim 22 (two corrections)) to clarify the claim language.

In response, applicants have amended claims 17 and 22 in accordance with the Examiner's proposals.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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